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DOI:

[10.1017/S0033291718000302](https://doi.org/10.1017/S0033291718000302)

Document Version

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Citation for published version (APA):

Ayerbe, L., Forgnone, I., Foguet-Boreu, Q., González, E., Addo, J., & Ayis, S. (2018). Disparities in the management of cardiovascular risk factors in patients with psychiatric disorders: a systematic review and meta-analysis. *Psychological Medicine*, 48(16), [PSM-D-17-00691R1]. <https://doi.org/10.1017/S0033291718000302>

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Disparities in the management of cardiovascular risk factors in patients with psychiatric disorders; a systematic review and meta-analysis

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Word count: 2952

Funding

Salma Ayis was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guys and St Thomas NHS Foundation Trust and Kings College London. Luis Ayerbe is funded by an NIHR Clinical Lectureship. This article therefore presents independent research funded by the NIHR. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. This project was conducted with no direct involvement from funders.

Abstract

Background: The high cardiovascular morbidity and mortality reported for patients with psychiatric disorders may possibly be due to a poorer management of cardiovascular risk factors. However, these healthcare disparities remain poorly understood. In this paper, studies comparing the management of smoking, diabetes, hypertension, and dyslipidaemia, in patients with and without depression, anxiety, schizophrenia, bipolar, or personality disorder, were reviewed.

Methods: Prospective studies comparing rates of screening, diagnosis, treatment and control of cardiovascular risk factors, were searched in PubMed, Embase, PsychInfo, Scopus, and Web of science (inception to January 2017). The Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were used. Studies were assessed for quality. Wherever possible, metanalyses were conducted to summarise the findings.

Results: Twenty studies, out of the 18333 references initially identified, were included. Most studies were heterogeneous in design. Two areas permitted metanalyses: the pooled OR for quitting smoking for those with depression, was 0.64(0.49 - 0.80) $p<0.001$; the pooled difference of glycated haemoglobin for patients with Type II diabetes and depression was 0.18(0.06-0.31) $p=0.005$. Individual studies showed associations between: schizophrenia and lower probability of having smoking habit recorded; schizoid personality disorder and higher probability of remaining non-smokers after quitting; anxiety and poorer control of Type I diabetes; depression, anxiety, or schizophrenia and lower probability of having a diagnosis of hypertension; schizophrenia or bipolar disorder and lower use of antihypertensive and lipid lowering drugs.

Conclusions: A proactive clinical management, together with further studies, are needed to reduce the cardiovascular morbidity and mortality of patients with psychiatric disorders.

Introduction:

The life expectancy of patients with mental health disorders is reduced between one and 32 years.(Colton and Manderscheid 2006, Viron and Stern 2010, Walker et al. 2015) A number of metaanalyses have reported in those with psychiatric conditions an increased frequency of cardiovascular risk factors (CVRFs), that varies for different patients and can be 27% higher for hypertension among those with bipolar disorders, to six times higher for smoking in those with schizophrenia, compared to those without each mental disorder.(Meng et al. 2012, Vancampfort et al. 2016, Jiang et al. 2014, Pan et al. 2015, de Leon and Diaz 2005, Chaiton et al. 2009, Vancampfort et al. 2015, Ayerbe et al. 2018) Strong evidence, also shows that those with psychiatric disorders, have higher incidence of cardiovascular (CV) diseases, that can be 34 to 71% higher for those with depression or schizophrenia respectively, compared to those without each disorder, and are the biggest contributor to the premature death of these patients.(Colton and Manderscheid 2006, Viron and Stern 2010, Walker et al. 2015, Van der Kooy et al. 2007, Roest et al. 2010, Pérez-Piñar et al. 2017, Fan et al. 2013, Prieto et al. 2014, Meng et al. 2012, Vancampfort et al. 2016, Jiang et al. 2014, Pan et al. 2015, de Leon and Diaz 2005, Wu and Kling 2016, Dong et al. 2012) A relevant and modifiable factor that could explain the high CV morbidity and mortality of those with psychiatric disorders is that they probably have poorer access to healthcare, including adequate management of CVRFs. (Kaufman et al. 2012, Viron and Stern 2010) How these disparities in healthcare may affect the management of different CVRFs for those with different mental health disorders is however poorly understood. It is also unclear at what stage of the care pathway, screening, diagnosis, treatment, or control, these disparities happen. Previous reviews addressing the potential disparities in preventive care among patients with psychiatric disorders have not used a comprehensive approach to CVRFs,

focused on specific psychiatric disorders, or presented only narrative summaries of the literature.(De Hert et al. 2011, J. B. Baller et al. 2015, Mitchell et al. 2009, Mangurian et al. 2016) Therefore, it remains difficult for clinicians, researchers, and policy makers to design evidence based interventions that effectively prevent premature CV diseases for people with psychiatric disorders. Stronger evidence on the differences in healthcare of each CVRF affecting specific psychiatric patients would help to correct disparities. It would allow focusing clinical resources on the most vulnerable individuals, and the management of the CVRF could become better targeted, more timely, feasible, and effective. A good understanding of the disparities of CV care could also inform future clinical trials of innovative interventions aiming to reduce the incidence of CV diseases among psychiatric patients with poorest access to healthcare. Finally, the management of CVRFs informed by stronger evidence in this area would become more cost effective with potential savings in acute CV care. All of these should potentially result in an effective and sustainable reduction of CV morbidity and overall mortality for psychiatric patients.

This review will test the following hypothesis: Patients with specific psychiatric disorders, compared to those without them, have poorer care of different CVRFs. In this paper we review the studies that compare the management of smoking habit, diabetes, hypertension, and dyslipidemia, in patients with and without depression, anxiety, schizophrenia, bipolar, or personality disorder.

Methods

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were used to undertake this review (Supplement 1).(Stroup et al. 2000) Electronic searches were conducted in

PubMed, Embase, PsycINFO, Scopus, and the Web of Science, from database inception to the 25th of January 2017.

We aimed to identify studies in compliance with the following inclusion criteria:

- 1) Observational prospective studies reporting original research data
- 2) Studies presenting differences in rates of screening, diagnosis, follow up, treatment, or control of smoking habit, diabetes, hypertension, or dyslipidaemia, for patients with and without each of the following mental disorders: depression, anxiety, schizophrenia, bipolar or personality disorder, identified with a validated scale or clinical assessment.

Studies were excluded if they were:

- 1) Conducted in specific patient sub-populations (e.g. patients receiving specific medication)
- 2) Interventional studies.
- 3) Only presented results of univariate analyses.
- 4) Using composite exposures (e.g. affective disorders) unless separate results for each of them were presented.
- 5) Exposure analysed as continuous variable (e.g. score in a depression scale instead of a medical diagnosis, or a validated score above a cut-off point, which are the methods for categorisation commonly used in clinical practice)('Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: Management in primary, secondary and community care' 2011, 'Depression in adults: The treatment and management of depression in adults' 2009)
- 6) Exposure presented as syndromes rather than distinct diagnoses (e.g. hallucinations), which are the categories from the commonly used by clinicians who manage CVRFs. (*Diagnostic and Statistical Manual of Mental Disorders (5th edition)* 2013)

7) Reporting a composite outcome unless separate results for each of its component had been provided (e.g. differences in the management of metabolic syndrome). The reason not to include composite outcomes is because, according to guidelines, clinicians have to care for each and every CVRF, therefore understanding the disparities affecting the management of each individual one of them is clinically relevant. ('Hypertension in adults: diagnosis and management' 2016, NICE 2017c, NICE 2017a, 'Nice Pathways. Cardiovascular disease prevention ' 2016, NICE 2017b)

The search strategy is presented in Supplement 2. Given the large number of CVRFs and psychiatric disorders reviewed in this paper only standard terms for searching were used. The titles and abstracts of all the references identified in the initial search were checked by one doctor (LA) against inclusion criteria. The bibliography of all papers fitting the inclusion criteria and relevant reviews was checked for further articles. Papers citing all the included studies, or relevant reviews were also searched in the Web of Science and considered for inclusion. There were no restrictions on the basis of language, sample size or duration of follow-up. Authors of the studies were contacted in some cases for further results or for clarifications in the ones presented. Two doctors extracted the data from the included studies (LA, IF, QFB, EG and/or JA). A standardized data-collection form was used to record author and publication year, country, number of participants, psychiatric disorder and measure, follow up, proportion of male and female participants, age, outcome and measure of association. The risk of bias and overall methodological quality of the studies fitting the inclusion criteria was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institute of Health (USA) (Supplement 3).('Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies' 2016) In some cases, similarities between studies indicated the possibility of

multiple publications from the same cohort. In the absence of explicit cross-referencing, we considered articles to be from the same cohort if there was evidence of overlapping recruitment sites, study dates and grant funding numbers, or there were similar reported patient characteristics in the studies.

Statistical analysis

When three or more studies with similar design, observed the same exposures and outcomes, metanalyses were considered possible, and the best way to summarise these associations. (Higgins 2008, Dwyer et al. 2001) When metanalyses were conducted, pooled estimates of differences were obtained, using random effects models. (DerSimonian and Kacker 2007) The heterogeneity between studies was measured using I-squared index, that represents the percentage of the total variation which is due to heterogeneity rather than chance. (Higgins et al. 2003) With the exception of one study, that reported hazard ratio (HR) for the association between depression and smoking, all other studies reported Odds ratios (OR) for the associations. (Anda et al. 1990) In that one HR was used in the meta-analysis as a proxy for OR. (Steele 2005) When studies on smoking cessation reported the final results as ratios of not quitting, these estimates were reversed to quitting. Confidence intervals were calculated using the formula described by Altman for one study that reported only p-values. (Musselman et al. 2014, Altman and Bland 2011) When a study reported results from a multivariable model exploring the differences of management of CVRFs for patients with and without psychiatric disorders, and then further modeling had been conducted to explore potential explanatory factors for these differences, only the results from the first model were included in the meta-analysis. Alternatively, when a study reported results from a preliminary analysis and then further adjustment was conducted to reach a model considered

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final by the authors, only the result of the later analysis were included in the meta-analysis. If a study presented associations between minor and major depression, as an outcome, only the associations with major depression were included in the meta-analysis. Where a study reported gender specific but not combined estimates, the results for each gender were included in the meta-analysis separately. We did not test for possible publication bias and small study effect formally, due to the small number of studies observing similar exposures and outcomes, that makes most formal tests inappropriate.(Borenstein et al. 2009) All statistical analyses were conducted using the software STATA version 14. The studies that reported other CVRFs (not smoking cessation and Type 2 Diabetes) among patients with other psychiatric disorders (not depression) were either not enough in number or too heterogeneous in design to be included in a meta-analysis, therefore their results are summarized narratively.

Results

The electronic search retrieved 16101 articles, eighteen of which were reviews relevant to the topic.(Julia B. Baller et al. 2015, Leucht et al. 2007, Mangurian et al. 2016, Egede and Dismuke 2012, George et al. 2012, Lustman et al. 2000, Hitsman et al. 2003, de Groot et al. 2001, Chen et al. 2016, Heffner et al. 2011, Lord et al. 2010, Mitchell et al. 2012, M et al. 2011, Mitchell et al. 2009, Oud and Meyboom-de Jong 2009, McGinty et al. 2015, J. B. Baller et al. 2015, Mitchell et al. 2015) The papers assessed at each stage of the search are presented in Figure 1. No papers written in languages other than the ones understood by the authors were identified at any time. The full text version of 165 papers was examined. Finally 20 studies were included in the review. They were all considered to be of good quality, with score ≥ 8 in the 14 items quality checklist.('Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies')

2016) Most studies were heterogenous in designs and observed different exposures in patients with different psychiatric disorders therefore were summarized narratively. However, the similarities in design, exposures, and outcomes, made possible to undertake two meta-analyses, of studies that reported associations between depression and management of smoking cessation, and between depression and Type 2 Diabetes.

Smoking

Eight studies including 9835 participants, conducted in Canada, the USA, Australia, the Czech Republic, France, Spain, and the UK, used smoking habit as an outcome (Supplement 4). Follow up was between one and nine years, and one study included only adolescent participants.(Zhu et al. 1999) Six studies compared patients with and without depression, which was recorded from results of four scales or was self-reported by participants.(Anda et al. 1990, Breslau et al. 1998, Stepankova et al. 2013, Zhu et al. 1999, Cooper et al. 2016, Fond et al. 2013) The outcome in all six was the proportion of patients who quit smoking which was significantly lower for those with depression in four of the studies. The pooled OR for quitting smoking for those with depression, compared to those without, was 0.64 (0.49 - 0.80) $p < 0.001$, and there was evidence of moderate heterogeneity across the six studies, I-squared 56.8%, $p = 0.031$ (Figure 2) It was acknowledged that two studies used reports from patients as measures of depression. These are subjective measures and can introduce bias.(Cooper et al. 2016, Stepankova et al. 2013) One of them caused the heterogeneity of the results as it reported a much stronger association with a smaller OR compared to the other studies.(Cooper et al. 2016) Removing this study from the metanalysis, resulted in the remaining studies being homogeneous with I-square equating to zero,

while the association between depression and giving up smoking remained significant, with an overall OR of, 0.74 (0.62 – 0.85) $p < 0.001$.

One study reported that patients with a medical diagnosis of schizophrenia were less likely to have their smoking habit in their medical records compared to those with no diagnosis. (Roberts et al. 2007) Finally, one study used personality disorders as a mental condition of interest, which was assessed with a questionnaire, and reported that the Schizoid Personality disorder was associated with higher rates of maintenance of abstinence after quitting. Other specific personality disorders, or the whole category of personality disorders, showed no association with abstinence after quitting. (Pineiro et al. 2013)

Diabetes mellitus

Two studies, conducted in the The Netherlands and the USA, including 422 participants, comparing control of Type 1 Diabetes, using reduction in glycated hemoglobin (HbA1c) levels as an indicator of good management, were identified (Supplement 5). (Hilliard et al. 2011, Bot et al. 2013) One of them included participants aged 13-18 (Hilliard et al. 2011) while the other one assessed participants equal or above 18 years of age. (Bot et al. 2013) Follow up was for one year in both of them and they reported the absence of an association between depression (measured with two scales), and diabetes control. However, one of them also reported that anxiety (measured with a scale), was associated with significantly poorer diabetes control at follow up. (Hilliard et al. 2011)

Five studies, conducted in Germany, The Netherlands and the USA, including a total of 20661 participants, looking at management of Type 2 Diabetes, were identified (Supplement 6). (Richardson et al. 2008, Heckbert et al. 2010, Bot et al. 2013, Kostev et al. 2016, Musselman

et al. 2014) Follow up ranged between three months and ten years. In one study 97% of participants were men.(Richardson et al. 2008) All of them compared patients with and without depression, which was recorded from the results of two scales, and from medical notes. Four studies investigated the association between depression and levels of HbA1c at follow up.(Richardson et al. 2008, Musselman et al. 2014, Bot et al. 2013, Heckbert et al. 2010) Three of these studies expressed control of Type II diabetes as percentage of HbA1c, and were included in a metanalysis. The pooled difference of HbA1c% at follow up between those with and without depression at baseline, across the three studies, was 0.18 (0.06 - 0.31) $p = 0.005$, with an I-squared of 41.1%, $p = 0.18$ (Figure 3). Another study compared for those with and without depression, the control of Type II diabetes, as mmol per mol of HbA1c, and could not be included in the metanalysis together with the other three.(Bot et al. 2013) In the later study no significant association between depression and control of Type II Diabetes was observed. Finally, one study reported that depression was associated with higher risk of insulin discontinuation.(Kostev et al. 2016)

Hypertension

Seven studies conducted in the USA, Denmark, Finland, and the UK, including a total of 1296899 participants, observed the management of hypertension (Supplement 7). Follow up ranged between one and 35 years. Four studies compared patients with or without depression, three used schizophrenia for comparison, one study used anxiety disorders, and another study compared those with and without bipolar disorder. One study showed that those with depression or anxiety were more likely to have a second blood pressure (BP) reading after having one showing high BP, but less likely to have a hypertension record after having two high BP

readings, compared to those without depression or anxiety.(Byrd et al. 2012) Another study reported that depression was associated with lower probability of receiving hypertension treatment,(Wang et al. 2005) while a different study found no differences.(Goldberg et al. 1980) Finally, depression was associated with lower rate of hypertension control only for women in one of the three sites where a multicenter study was conducted.(Simonsick et al. 1995) One study showed that patients with schizophrenia were less likely to have their BP recorded,(Roberts et al. 2007) and two studies showed lower use of antihypertensive drugs in these patients,(Lahti et al. 2012, Laursen et al. 2014) although in one of them schizophrenia patients were more likely to have diuretics.(Laursen et al. 2014) Finally, those with bipolar disorders were reported to be less likely to receive angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, but more likely to have diuretics, calcium channel blockers and beta blockers.(Laursen et al. 2014)

Dyslipidaemia

Three studies, conducted in Denmark, Finland, and the UK, including a total of 1073032 participants, reported the management of dyslipidaemia (Supplement 8). Follow up ranged from three to 35 years. Patients with and without schizophrenia were compared in all three studies and one of these additionally compared those with and without bipolar disorder. Data on schizophrenia or bipolar disorder were collected from medical records. Schizophrenia was associated with a lower probability of having cholesterol recorded in one study,(Roberts et al. 2007) while two studies reported that these patients were less likely to use lipid lowering drugs.(Lahti et al. 2012, Laursen et al. 2014) Those with bipolar disorder were also observed to be less likely to use lipid lowering drugs.(Laursen et al. 2014)

Discussion

A limited number of studies of good quality have investigated the differences of the management of major CVRFs among patients with specific psychiatric disorders. Our metaanalyses show that patients with depression have lower probabilities of giving up smoking, and also poorer control of Type 2 Diabetes, compared to those without depression. Few studies have reported other disparities in the management of CVRFs: those with schizophrenia are less likely to have their smoking habit recorded; schizoid personality disorder is associated with patients remaining nonsmokers after giving up; anxiety, but not depression affects the control of Type 1 Diabetes; those with depression, anxiety, or schizophrenia are less likely to have a diagnosis of hypertension ; patients with schizophrenia or bipolar disorder use less antihypertensive and lipid lowering drugs.

The disparities in care for CVRF among patients with mental health issues observed in this review are in line with the results of previous narrative reviews that have approached specific groups of psychiatric patients or wider areas of healthcare.(De Hert et al. 2011, J. B. Baller et al. 2015, Mitchell et al. 2009, Mangurian et al. 2016)

A number of factors affect the CV care of patients with mental health disorders and may explain the disparities observed in this review. Psychiatric symptoms can disrupt the process of healthcare, for example lack of motivation leads to poor attendance of appointments, thought disorder can complicate the process of taking a clinical history, and agitation, or social phobia may make it difficult for the patient to report his problems clearly.(Viron et al. 2012) Many people with psychiatric conditions also have a substance use disorders, which interfere with treatment adherence and efficacy.(Viron and Stern 2010) The medication used to treat psychiatric disorders can have negative effects on control of CVRFs as well. Associations

between antidepressants and higher risk of diabetes, hypertension, and hyperlipidemia, and between antipsychotics and dyslipidaemia, and diabetes, have been reported..(Correll et al. 2015, Perez-Pinar et al. 2016) A strong association particularly between atypical antipsychotics, such as olanzapine, clozapine, quetiapine or risperidone, and diabetes has been observed.(Correll et al. 2015) Furthermore, some clinicians feel uncomfortable with these patients because of limited experience or resources and this can also lead to a poor care of CVRFs. Stigmatization of psychiatric patients is common, not only among the general public but also among clinicians.(Kaufman et al. 2012) In addition, some doctors may underestimate patients as capable partners in their own care.(Viron and Stern 2010) It has been reported that those with mental disorders feel that clinicians take their physical symptoms less seriously once the psychiatric diagnosis is revealed.(Viron et al. 2012) The organization of the health service may represent another obstacle to healthcare, that can explain the disparities in the management of CVRF for people with mental disorders. The fragmentation of the health service between primary care and psychiatry makes the coordination of care particularly challenging.(Kaufman et al. 2012) Finally, in countries without universal access to healthcare those with psychiatric problems are more likely to have financial barriers to access healthcare than those without mental health issues.(Viron and Stern 2010, Kaufman et al. 2012) All these factors can contribute to the poorer management of CV risk in those with psychiatric disorders, and explain the findings of this review.

This review has some limitations. Only one doctor screened the initial list of references (LA). Since only studies assessing psychiatric disorders categorically were included, large population-based studies using continuous measures for assessment, or overlapping constructs (e.g. psychosis), might have been missed, which limits the external validity of this review. The

diversity of the methods across studies, including the different statistical management, may have an effect on the external validity of each individual one. Another limitations is that, the heterogeneity of many studies made impossible to obtain mathematical summaries of healthcare disparities, that could have aided clinical and health policy decisions. While these pooled estimates were obtained on studies observing similar psychiatric disorders and CVRFs, the low number of these studies did not allow to analyse for possible publication bias.(Borenstein et al. 2009) Finally, the exclusive use of standar terms for searching, which can lead to some relevant studies being missed, may represent a limitation of this review. However, the comprehensive search, that included electronic searches in five different databases, hand searches, backward and forward citation searching, and had no restrictions on the basis of language, sample size or duration of follow-up, substantially reduces the chances of missing relevant studies, and represents a strength of this paper. This paper has other strengths as well. The association between depression and both smoking and control of Type 2 diabetes, were obtained on a fairly large number of patients. The use of a random effect model based on the assumption that studies were independently conducted and do not necessarily share a common effect size, allowing for more uncertainty of the final summary estimate, was a conservative choice.

Clinicians should be aware that those with depression are less likely to quit smoking and to have good control of Type 2 Diabetes. Since depression is a manageable condition, screening for it with a brief and reliable tool all patients who are going to receive treatment for smoking cessation or Type 2 Diabetes could be recommended.(Mitchell et al. 2016) Doing this could lead to the management and improvement of low mood and to higher rates of smoking cessation and diabetes control. Clinicians should also be particularly proactive in the care of CVRFs in all psychiatric patients, as the available studies suggest that it is substandard. However, the evidence

on the disparities on CV care for patients with psychiatric disorders is still very limited. For many psychiatric patients it remains unknown when and where along the care pathway they lose access to clinical care of good quality. The evidence is particularly poor for those with anxiety, bipolar, or personality disorders. More studies are needed to understand where the healthcare disparities happen, for those with a variety of psychiatric problems. Future investigations on healthcare disparities could consider comparing differences in outcomes defined by guidelines as the main steps of CV prevention (screening, diagnosis, treatment, follow up and control of CVRF).('Nice Pathways. Cardiovascular disease prevention ' 2016) Such studies could inform innovative interventions to improve the CV care, and ultimately reduce the CV morbidity and overall mortality, of patients with psychiatric disorders.

Disclosure of interest

The authors declare that they have no competing interest.

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